RADIATION RESEARCH **159**, 787–798 (2003)
0033-7587/03 $5.00

Cancer Mortality Risk among Workers at the Mayak Nuclear Complex

N. S. Shilnikova,[a] D. L. Preston,[b,1] E. Ron,[c] E. S. Gilbert,[c] E. K. Vassilenko,[d] S. A. Romanov,[a] I. S. Kuznetsova,[a] M. E. Sokolnikov,[a] P. V. Okatenko,[a] V. V. Kreslov[a] and N. A. Koshurnikova[a]

[a] *Southern Urals Biophysics Institute, Ozyorsk, Russia;* [b] *Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan;* [c] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; and* [d] *Department of Radiation Safety, Mayak Production Association, Ozyorsk, Russia*

Shilnikova, N. S., Preston, D. L., Ron, E., Gilbert, E. S., Vassilenko, E. K., Romanov, S. A., Kuznetsova, I. S., Sokolnikov, M. E., Okatenko, P. V., Kreslov, V. V. and Koshurnikova, N. A. Cancer Mortality Risk among Workers at the Mayak Nuclear Complex. *Radiat. Res.* 159, 787–798 (2003).

At present, direct data on risk from protracted or fractionated radiation exposure at low dose rates have been limited largely to studies of populations exposed to low cumulative doses with resulting low statistical power. We evaluated the cancer risks associated with protracted exposure to external whole-body γ radiation at high cumulative doses (the average dose is 0.8 Gy and the highest doses exceed 10 Gy) in Russian nuclear workers. Cancer deaths in a cohort of about 21,500 nuclear workers who began working at the Mayak complex between 1948 and 1972 were ascertained from death certificates and autopsy reports with follow-up through December 1997. Excess relative risk models were used to estimate solid cancer and leukemia risks associated with external γ-radiation dose with adjustment for effects of plutonium exposures. Both solid cancer and leukemia death rates increased significantly with increasing γ-ray dose ($P < 0.001$). Under a linear dose–response model, the excess relative risk for lung, liver and skeletal cancers as a group (668 deaths) adjusted for plutonium exposure is 0.30 per gray ($P < 0.001$) and 0.08 per gray ($P < 0.001$) for all other solid cancers (1062 deaths). The solid cancer dose–response functions appear to be nonlinear, with the excess risk estimates at doses of less than 3 Gy being about twice those predicted by the linear model. Plutonium exposure was associated with increased risks both for lung, liver and skeletal cancers (the sites of primary plutonium deposition) and for other solid cancers as a group. A significant dose response, with no indication of plutonium exposure effects, was found for leukemia. Excess risks for leukemia exhibited a significant dependence on the time since the dose was received. For doses received within 3 to 5 years of death the excess relative risk per gray was estimated to be about 7 ($P < 0.001$), but this risk was only 0.45 ($P = 0.02$) for doses received 5 to 45 years prior to death. External γ-ray exposures significantly increased risks of both solid cancers and leukemia in this large cohort of men and women with occupational radiation exposures. Risks at doses of less than 1 Gy may be slightly lower than those seen for doses arising from acute exposures in the atomic bomb survivors. As dose estimates for the Mayak workers are improved, it should be possible to obtain more precise estimates of solid cancer and leukemia risks from protracted external radiation exposure in this cohort.

INTRODUCTION

At present, radiation risk estimates used as a basis for radiation protection standards are derived from data on persons exposed externally at high doses and high dose rates, including the atomic bomb survivors in Hiroshima and Nagasaki and many medically exposed cohorts (*1–4*). There naturally are concerns about the relevance of these data for estimating risks from exposure at low doses and dose rates, which are of primary interest for radiation protection. Direct data on risk from protracted or fractionated exposure at low dose rates mainly have been limited to studies of populations (such as nuclear workers) exposed to low cumulative doses with resulting low statistical power and high potential for confounding.

The Mayak Production Association, which is located in the Southern Urals in the Russian Federation, about 100 km from the city of Chelyabinsk, began operations in 1948 as the first and largest nuclear weapons facility in the former Soviet Union. A substantial number of workers at the Mayak facility, especially those employed in the first decade of operation, received cumulative doses that far exceed those of nuclear workers in other countries. Thus these workers offer an unusual opportunity to study the effects of protracted whole-body exposure at cumulative doses that are sufficiently large to estimate risks with some degree of precision. The Mayak worker cohort is unique among cohorts used to study radiation effects because it includes a large proportion of women (24%) whose average doses are similar to those for men. The cohort has been described in several publications (e.g. refs. *5–7*). Quantitative estimates of cancer mortality risks associated with chronic low-dose-rate exposure at Mayak can be an important complement to estimates of the effects of acute exposures derived from

[1] Address for correspondence: Department of Statistics, 5-2 Hijiyama Koen, Minami ku, Hiroshima 730-0045, Japan; e-mail: preston@rerf.or.jp.

TABLE 1
Description of the Extended Mayak Worker Cohort by Primary Work Place

Type of radiation exposure[a]	Reactors	Radiochemical	Plutonium production	Auxiliary plants	Total
	External	External and internal	External and internal	Relatively low external and internal	
Number of workers (percentage female)	4,396 (22%)	7,892 (25%)	6,545 (27%)	2,724 (19%)	21,557 (24%)
Average age at hire	24.5	23.9	24.5	23.4	24.2
Average year of hire	Dec 1954	May 1955	March 1957	Jan 1960	May 1956
Number monitored for external radiation[b] (%)	3,882 (88%)	7,626 (97%)	4,153 (63%)	1,496 (55%)	17,157 (80%)
Average cumulative whole-body external γ-ray dose (Gy)	0.66 (0.37/8.5)[c]	1.21 (0.61/11.3)	0.44 (0.11/7.3)	0.17 (0.07/7.9)	0.81 (0.31/11.3)
Monitored for plutonium body burden (%)	167 (4%)	2,706 (34%)	2,458 (38%)	0 (0%)	5,331 (25%)
Average plutonium body burden (kBq)	0.2 (0/5.1)[c]	1.2 (0.5/75)	3.3 (0.35/172)	—	2.1 (0.4/172)
Average cumulative internal lung dose (Gy)	0.01 (0/0.4)[c]	0.06 (0.02/3.3)	0.32 (0.02/18.7)	—	0.18 (0.02/18.7)

[a] External exposure is predominantly from γ rays and is determined from film badge monitoring records. Internal exposures arose primarily from the inhalation of plutonium aerosols. Body burden and dose estimates are based on the urine excretion measurements that were obtained for monitored workers.

[b] Unmonitored workers were believed to have little likelihood of external exposure.

[c] Median/maximum γ-ray dose, lung dose, or plutonium body burden.

the Life Span Study of the Japanese atomic bomb survivors (*1*).

This is the first paper to present leukemia and solid cancer risk estimates for the full Mayak nuclear worker cohort. The paper focuses on estimates of the effects of external exposure with adjustment for the effects of internal exposures. Previous estimates of lung cancer risks associated with external γ-ray exposures and internal exposures to plutonium were based on a small subset of the cohort (*8–12*). Descriptions of the effect of internal exposures on cancer rates in liver (*13*) and bone (*14*), and discussion of the effects of external exposures on cancer rates in portions of the cohort have been published (*5, 15*).

MATERIALS AND METHODS

This record-based epidemiological study required no contact with the cohort members. The project was reviewed and approved by the Institutional Review Boards of the participating institutions.

Cohort Definition

The original cohort includes all people (about 18,800) who worked in one or more of Mayak's three main facilities (nuclear reactor complex, radiochemical plant, and plutonium production plant) and who were hired in 1948 to 1972. This cohort has recently been extended to include 2,700 people who worked only in auxiliary plants (water treatment facility and mechanical repair plant). The extended cohort includes all people hired during this period who worked in either the main facilities or the selected auxiliary plants. This includes all workers with a potential for significant external radiation exposure and a large number of workers with little or no exposure. Table 1 summarizes characteristics of the Mayak worker cohort. The average cumulative external dose among those monitored for external radiation exposures was 0.8 Gy. Approximately 25% of the members of the Mayak worker cohort are women. Their average dose is similar to that received by male workers. Workers in all three main facilities were exposed externally to γ rays, and workers in the radiochemical and plutonium production plants also had potential for significant internal exposures from inhaled plutonium aerosols. Auxiliary plant workers had relatively low exposures, but even these workers received larger average doses of external γ radiation than workers in other countries (*16*).

Follow-up

Vital statistics data (including death certificates and autopsy reports) and address bureau records are monitored to determine the vital status and cause of death for cohort members who still reside in Ozyorsk. When a person moves to another region, the address bureau record indicates the new region, making it possible to trace cohort members who have left Ozyorsk. Address bureau records are maintained for 5 years after a person dies or migrates from the region, and they provide information on current vital status, date and place of migration, and date and place of death. When a person has died, the death certificate is obtained, and the underlying cause of death is coded using ICD-9 codes (*17*). A 10% sample of the deaths is recoded to assess the quality of the coding. In recent years a systematic program of recoding has been developed to monitor and improve the quality of the cause-of-death coding.

Coding of the underlying cause of death is based on information from various sources including death certificates and autopsies, with preference given to autopsy findings when such information was available. Information from autopsies was used in the determination of the underlying cause for 46% of deaths in Ozyorsk. However, such information is available for only 1% of the deaths occurring among cohort members who died outside Ozyorsk. Autopsies were carried out more frequently for radiochemical or plutonium plant workers than for people who worked in the reactor complex or auxiliary departments, for workers monitored for plutonium body burden, and for those with higher potential for plutonium exposure. However, the use of autopsy information in the determination of cause of death has little impact on the assigned cause (*6*).

Follow-up for analyses in this paper begins at the time the person began working at Mayak and continues through the earliest of the date of loss to follow-up, death or December 31, 1997. As indicated in Table

TABLE 2
Follow-up Status for the Extended Mayak Worker Cohort as of December 31, 1997

By subcohort: original cohort (main plants) and extension (auxiliary plants)	Main plants	Auxiliary plants	Total
Number of workers	18,833	2,724	21.557
Mean age at end of follow-up	61.9	56.6	61.2
Number of deaths	6,352	715	7,067
Solid cancer deaths	1,588	142	1,730
Leukemia deaths[a]	74	3	77
Unknown cause of death	161 (2.5%)	52 (7.3%)	213 (3.0%)
Lost to follow-up	1,925 (10.2%)	260 (9.5%)	2,185 (10.1%)
By gender	**Male**		**Female**
Number of workers	16,291		5,266
Mean age at end of follow-up	59.3		65.8
Number of deaths	5,852		1,215
Solid cancer deaths	1,381		349
Leukemia deaths[a]	60		17
Unknown cause of death	186 (3.2%)		27 (2.2%)
Lost to follow-up (%)	1,738 (10.7%)		447 (8.5%)

[a] Including 11 chronic lymphocytic leukemia (CLL) deaths that were excluded from the primary analyses.

2, vital status as of December 31, 1997 is known for 90% of the cohort members, and tracing rates are similar for the main and auxiliary plant workers. However, the percentage of deaths for which the cause is unknown is somewhat greater for the auxiliary plant workers.

Dosimetry

Film-badge monitoring for external radiation started at the inception of Mayak operations and has been carried out for all workers with potential for such exposure. Unmonitored workers held jobs or worked in departments that had little potential exposure. Since analyses (not shown) of baseline cancer rates provide no evidence that unmonitored workers had higher cancer risks than monitored workers with very low doses, unmonitored workers were treated as having an external dose of 0 Gy. Four types of individual dosimeters were used over time. In the earliest period (1948–1953), film dosimeters had no compensating filters, which resulted in exposure of the film to high-energy β particles. This led to overestimation of the external γ-radiation dose for workers at some workplaces (*18*). The dosimeters used in later periods did not have this problem and appear to provide consistent and accurate dose estimates. Efforts are currently under way to improve external dose estimates. Our analyses are based on uncorrected individual annual dose estimates abstracted from archival records at Mayak. Doses from external γ radiation were high in the late 1940s and early 1950s at all of the main plants, and they decreased over the years. For example, the mean estimated cumulative doses for workers hired in 1948–1953, 1954–1958 and 1959–1972 were 1.3, 0.5 and 0.2 Gy, respectively. Although about 20% of the auxiliary plant workers had external radiation doses in excess of 100 mGy; most of these workers had little likelihood of external exposure (in which case they were not monitored) and hence had substantially lower doses.

In addition to external radiation exposures, workers at the radiochemical and plutonium production plants had potential for internal exposures from inhaled plutonium compounds. The major component contributing to internal exposure was the α-particle-emitting radionuclide ^{239}Pu (referred to as plutonium). Significant plutonium exposures occurred in the early years of Mayak operation because of poor working conditions. Major reductions in exposure levels were achieved after 1956 largely due to the introduction of individual respirators. As time went on, technological improvements (*18*) led to further reductions. A systematic program for monitoring workers' plutonium exposures began in 1970. This program involves direct measurement of plutonium in large urine samples. Body burden and annual organ dose estimates are based on a biokinetic model that uses information on exposure history and transportability of plutonium aerosols as inputs into models for lung clearance (*19–21*) and systemic plutonium excretion (*22*). Transportability of the plutonium aerosols at different work locations was measured by dialysis methods (*23*). Comparison of body burden estimates based on urine excretion data with values determined at autopsy indicate that there is considerable uncertainty but no substantial bias in the urine excretion-based body burden estimates (*21*). By the end of 1996, urine excretion data had been obtained for only 36% of those who worked in the radiochemical or plutonium production plants.

For the purposes of this paper, plutonium exposure is important primarily because of the need to adjust for it in evaluating the effects of external exposure. Human autopsy data and experimental animal studies show that the distribution of plutonium in the body is highly nonuniform, with deposition mainly in the lung, liver and skeleton (*24–26*). Since ^{239}Pu has a very long half-life (over 24,000 years), it results in continuous irradiation of exposed organs throughout life (*27*).

To estimate cancer risks from external γ radiation, adjusted for the effects of internal exposure, for the full Mayak worker cohort, including workers for whom plutonium monitoring data are not available, we developed a categorical surrogate index of plutonium exposure defined in terms of basic occupational history data, including work locations, starting dates, the distribution of measured body burden values, and expert knowledge of working conditions at various times in the different facilities. As shown in Table 3, mean body burden and lung dose estimates for monitored workers increase with increasing levels of the surrogate measure. The standard errors for body burden estimates make it clear that there is considerable variability among monitored workers with a given surrogate index level, especially for workers with the highest potential for plutonium exposure (levels 4 and 5). Because workers thought to have been at risk of exposure to the highest levels of plutonium were more likely to be selected for monitoring, it is inappropriate to regard the mean plutonium body burden (dose) for monitored workers as a representative value for all workers. All reported analyses are based on a four-level surrogate index created by combining levels 1 and 2 and levels 4 and 5. This modification resulted in little loss of information and had no appreciable influence on the primary results. Because of indications that some workers were monitored as a result of suspected diseases, people are treated as unmonitored for the first 2 years after the initial monitoring date.

Organization of Data for Analysis

For these analyses, the data were organized as a multi-way person-year table with classification by facility, gender, period of hire (four periods), plutonium surrogate index categories (six categories), and 5-year categories of attained age, age at hire, and calendar period. The table also included stratification on a time-dependent indicator of plutonium monitoring, time since initial monitoring, and estimated plutonium body burden. Time-dependent lagged cumulative external doses were jointly classified for lags of 2, 5 and, in some cases, 10 and 20 years. There were 15 categories for each lagged cumulative external dose: a category for unmonitored workers, a zero dose category, and 13 other categories with boundaries of 0.2, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6 Gy. With this joint classification, it is possible to use different lags for leukemia (2 years) and solid cancer (5 years) and to examine the temporal pattern of the dose response using time-dependent windows for doses received 3 to 5 years ago, 5 to 10 years ago, 10 to 20 years ago, and more than 20

TABLE 3
Plutonium Surrogate Index Definition with Summary Statistics

Level	Surrogate category definition	People	Percentage monitored for plutonium body burden	Plutonium body burden (kBq)	Cumulative lung dose (Gy)[a]
5	Plutonium production, main departments, hired 1948–1949	662	32%	18.5 ± 30[b]	1.92
4	Plutonium production, main departments, hired 1950–1953	250	34%	14.9 ± 30	1.43
3	Plutonium production, main departments, hired 1954–1958 Plutonium production, auxiliary departments, hired 1948–1949	1704	30%	2.9 ± 5.5	0.28
2	Plutonium production, main departments, hired 1959–1963 Plutonium production, auxiliary departments, hired 1950–1958 Radiochemical plant, hired 1948–1953	5239	35%	1.7 ± 4.3	0.11
1	Plutonium production, main departments, hired 1964–1972 Plutonium production, auxiliary departments, hired 1959–1972 Radiochemical plant, hired 1954–1972	6582	39%	0.6 ± 2.0	0.04
0	Reactor plants, hired 1948–1972 Auxiliary plants, hired 1948–1972	7120	2%	0.2 ± 0.5	0.01

[a] The lung dose from inhaled plutonium is computed from the estimated body burden using the biokinetic models described in refs. (*19–23*).
[b] Mean and standard deviation of estimated values for monitored workers.

years ago. The resulting person-year table has about 100,000 cells with non-zero person years. To investigate how differential autopsy rates affect risk estimates, we created a supplementary person-year rate table that included time-dependent stratification on place of residence (Ozyorsk or elsewhere). Slightly less than half of the cohort members have moved away from Ozyorsk (about 35% are still being actively followed and about 10% are lost to follow-up). Migrants account for about one-third of the total person years and 40% of the deaths seen to date.

Statistical Methods

Excess relative risk models were used to describe the risks. The basic model has the form $\lambda_0(a,s,z)\cdot[1+ERR(d)]$, where λ_0 () is the baseline hazard (rate) function, which varies with attained age (a), gender (s) and other covariates (z). $ERR(d)$ is the excess relative risk function, in which d involves both external dose and internal exposure as described below. The logarithm of the baseline hazard was modeled using gender-specific quadratic functions of log attained age with an effect to allow for different rates of death ascertainment for main and auxiliary plant workers. The dose response was described using models that allow for effects of both external (d_{ext}) doses and internal (d_{pu}) exposures. The dose response functions considered are:

$$ERR(d) = \begin{cases} \beta_{ext} d_{ext} + \gamma_{pucat} I_{unmon} + \beta_{pu} d_{pu} I_{mon} \\ \qquad \text{linear} \\ \beta_{ext,1} d_{ext} + \beta_{ext,2} d_{ext}^2 + \gamma_{pucat} I_{unmon} + \beta_{pu} d_{pu} I_{mon} \\ \qquad \text{linear-quadratic} \\ \beta_{extcat} + \gamma_{pucat} I_{unmon} + \beta_{pu} d_{pu} I_{mon} \\ \qquad \text{non-parametric} \end{cases}$$

The β's are parameters describing the external-dose and internal-exposure response slopes in terms of the time-dependent lagged cumulative doses, and the γ_{pucat} parameters are excess relative risk estimates for categories of the plutonium surrogate index. In most analyses, the surrogate index was used for periods during which there was no plutonium monitoring data ($I_{unmon} = 1$), while estimated plutonium body burden was used during post-monitoring periods ($I_{mon} = 1$) for monitored workers. However, we also considered models based solely on the surrogate index. Results for the linear-quadratic model are presented in terms of the limiting low-dose slope ($\beta_{ext,1}$) and the curvature of the dose response, which is defined as $\beta_{ext,2}/\beta_{ext,1}$. Parameters associated with plutonium surrogate categories were constrained to be non-negative. These ERR models were also extended to allow for factors such as age at hire, age at death, and gender to have multiplicative effects on the external dose portion of the response function.

When assessing the temporal variation in the ERR we used the following linear model,

$$ERR(a) = \sum_w \beta_w d_{w,ext}(a) + \gamma_{pucat} I_{unmon} + \beta_{pu} d_{pu} I_{mon},$$

in which $d_{w,ext}(a)$ is the external dose received in a specific period (exposure window) prior to the current time, e.g. 5 to 10 or 10 to 20 years prior to the current time; the β_w are the corresponding risk estimates.

Since the effects of internal exposure were more pronounced for tissues of primary plutonium deposition (lung, liver and skeleton), we separately adjusted for the effects of plutonium exposures for cancers of these sites and other solid cancers. We used the joint analysis methods described in ref. (*28*) to do this. In these analyses cause-specific person-year tables were concatenated to form a large combined dataset, background rate models were stratified on cause of death, and tests of the hypothesis that some or all of the excess risk parameters were equal for different causes were carried out. This method allowed us to carry out an explicit test of the hypothesis that the slope of the dose response differs for these two groups of solid cancer sites. A joint analysis with separate parameters for each type is equivalent to separate analyses for each type. So if, as was the case in these analyses, one rejects the hypothesis of a common dose–response slope, it is simplest to analyze the different end points separately.

Parameter estimates were computed with maximum likelihood methods. Hypothesis tests and confidence intervals were based on likelihood ratio tests and direct evaluation of the profile likelihood. The models were fitted using the Epicure software (*29*). Two-sided P values and 90% confidence intervals were used throughout. Since our primary interest concerns the one-sided hypothesis that radiation is associated with increased risks in this cohort, we chose to use 90% confidence intervals in which the upper bound corresponds to a one-sided 95% bound for the parameter of interest.

In addition to the parameter estimates, we present estimates of the expected and excess cases, with the excess apportioned between external and internal exposures derived from the fitted models. The expected number of cases (in the absence of exposure) was computed as the sum of the product of the fitted baseline rate and the number of person years divided by the cells in the detailed person-year table. The estimated number of excess cases for each record in the person-year table due to external exposures was computed as the product of the expected number of cases in the absence of exposure and the estimated external dose ERR, for

TABLE 4
Mayak Worker Cohort Cause-of-Death Distribution by Gender

Cause	Male		Female		Total
All deaths	5852		1215		7067
All cancer deaths	1475		379		1854
All solid cancers	1381		349		1730
Oral cavity	39	2.8%[a]	4	1.1%	43
Stomach	258	18.7%	50	14.3%	308
Colon	49	3.5%	19	5.4%	68
Rectum	49	3.5%	25	7.2%	74
Liver	44	3.2%	23	6.6%	67
Gallbladder	16	1.2%	10	2.9%	26
Pancreas	64	4.6%	9	2.6%	73
Other digestive	41	3.0%	9	2.6%	50
Lung	517	37.4%	52	14.9%	569
Other respiratory	53	3.8%	3	0.9%	56
Skeleton	21	1.5%	11	3.2%	32
Skin	18	1.3%	8	2.3%	26
Breast	0	0.0%	60	17.2%	60
Uterus	—	—	9	2.6%	9
Ovary	—	—	33	9.5%	33
Prostate	38	2.8%	—	—	38
Other male	5	0.4%	—	—	5
Bladder	39	2.8%	0	0.0%	39
Kidney	44	3.2%	8	2.3%	52
Eye	3	0.2%	1	0.3%	4
Brain and nervous system	41	3.0%	4	1.1%	45
Endocrine system	5	0.4%	2	0.6%	7
Other, ill-defined	2	0.1%	0	0.0%	2
Unknown	35	2.5%	9	2.6%	44
Hematopoietic cancers					
Total hematopoietic cancers	94		30		124
Leukemia (excluding CLL)	55		11		66
Chronic lymphocytic leukemia (CLL)	5		6		11
Non-Hodgkin's lymphoma	16		8		24
Hodgkin's lymphoma	11		2		13
Myeloma	7		3		10
Noncancer deaths					
Noncancer diseases	3259		728		3987
External causes	1118		108		1226

[a] Percentage of sex-specific solid cancers.

example $ERR = \beta_{ext} d_{ext}$ for a simple linear model. These estimates were then summed over the relevant cells. The estimated number of excess cases due to internal exposures was computed as the difference between the estimated total number of excess cases and the estimated number of excess cases associated with external exposure.

To evaluate the possibility of autopsy-related bias in our estimates of radiation effects, we compared cause-specific solid cancer mortality background rates for Ozyorsk residents and migrants and then tested for a radiation-by-migration effect on the external-dose ERR.

RESULTS

Cancer Deaths

For the period covered by these analyses, there were about 720,000 person years of follow-up, with 1,730 solid cancer deaths and 77 leukemia deaths in the Mayak worker cohort. The solid cancers included 668 deaths from cancers in the organs of primary plutonium deposition (569 lung cancers, 67 liver cancers, and 32 skeletal cancers) and 1062 deaths from other solid cancers. Details on the number of cancer deaths by site and gender are presented in Table 4. Among men, lung and stomach cancers were the most common fatal cancers. Breast cancer deaths were as common as lung or stomach cancer deaths among women in this cohort. Site could not be determined for about 2.5% of the deaths attributed to cancer. The leukemia deaths included 11 deaths attributed to chronic lymphocytic leukemia (CLL) and 66 deaths from other types of leukemia. CLL deaths were considered separately from the other leukemias, since it is generally thought that the risk of CLL is not associated with radiation dose (*30–33*).

Solid Cancer Mortality Dose Response

A pooled analysis of all solid cancer deaths using a linear dose–response model with adjustment for internal exposure

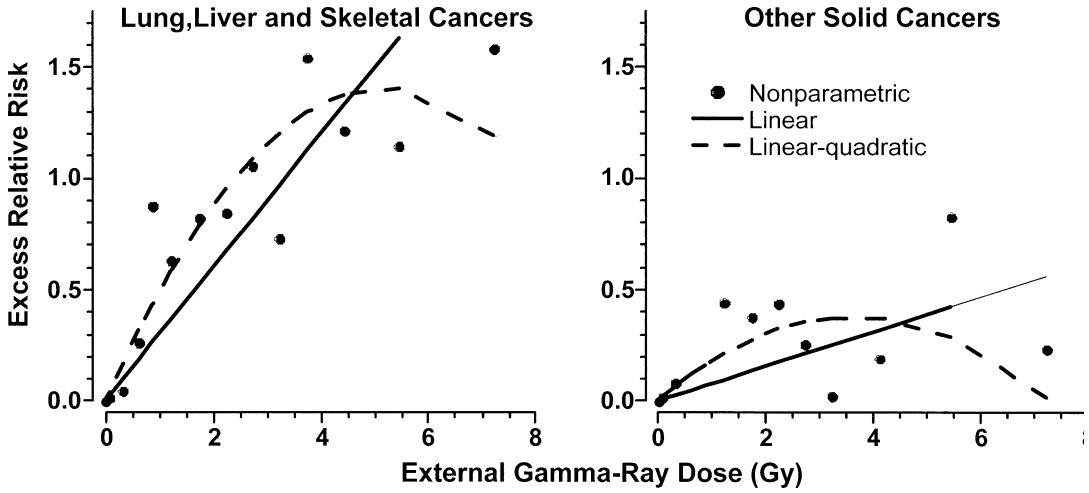

FIG. 1. Parametric and nonparametric descriptions of the external dose response for the solid cancer ERR in the Mayak worker cohort. The estimates are adjusted for internal exposure. There is significant nonlinearity for both groups considered, and for each group the low-dose slope for the linear-quadratic model is about twice the estimate from the linear model.

indicated a highly significant effect of 5-year lagged external dose on cancer risk ($P < 0.001$) with an ERR per gray estimate of 0.15 (90% CI 0.09; 0.20). However, there was also evidence of statistically significant non-linearity ($P = 0.01$) in the dose response. The fitted linear-quadratic dose response was concave downward with an estimated linear coefficient of 0.3 per gray (90% CI 0.18; 0.43), which is about twice that suggested by the linear model. The curvature was estimated as -0.12 (90% CI -0.14; -0.06). Exclusion of the auxiliary plant workers has little impact on point estimates of risk. Virtually identical results were obtained from a joint analysis that allowed for differences between the internal exposure effects for lung, liver and skeletal cancers and those for other solid cancers but assumed a common external exposure dose response for the two broad groups of cancer deaths. However, because the joint analysis provided evidence of a statistically significant difference ($P = 0.01$) between the external dose effects for these two groups of cancer deaths, these results are presented separately.

An examination of migration effects indicates that gender- and age-specific cancer rates for migrants were significantly lower ($P = 0.005$, SMR = 0.83, 90% CI 0.74; 0.92) than for Ozyorsk residents. However, there was no indication that the estimated ERR per gray depends on place of residence ($P = 0.5$). We also note that despite the lower cancer rates for migrants, there is no indication of a difference in death rates for all causes ($P > 0.5$, SMR = 1.01, 90% CI 0.96; 1.06), suggesting that the difference seen for solid cancers could reflect an increased likelihood of cancer being reported when an autopsy is performed rather than incomplete follow-up for migrants.

Lung, Liver and Skeletal Cancers

There was clear evidence of increased risks for lung, liver and skeletal cancers, as a group, associated with both external ($P < 0.001$) and internal exposures ($P < 0.001$), using either the surrogate index only or a combination of the surrogate index for unmonitored workers and body burden for monitored workers. There was also a suggestion ($P = 0.08$) of downward curvature in the external dose response in a linear-quadratic dose–response model. Under a linear model, the estimated excess relative risk was 0.30 per gray (90% CI 0.18; 0.46). The linear coefficient in the linear-quadratic model was 0.54 (90% CI 0.27; 0.89) per gray while the curvature is estimated to be -0.1 (90% CI <-0.13; -0.01). The left panel in Fig. 1 presents dose-category-specific ERR estimates and shows both the fitted linear and linear-quadratic dose–response functions. Exclusion of workers in the surrogate categories with the highest potential for plutonium exposure had no appreciable effect on these results.

There was no indication of migration/autopsy rate effects on either the background rates ($P > 0.05$, SMR = 0.95, 95% CI 0.78; 1.15) or the ERR per gray ($P = 0.16$).

Other Solid Cancers

For solid cancers other than those of the lung, liver and skeleton, a dose effect was observed for external exposures ($P < 0.01$). While there was little indication of internal exposure effects for these cancers based solely on the surrogate index ($P = 0.3$), the evidence for such effects was strengthened ($P < 0.001$) when the surrogate index is used for unmonitored workers in combination with body burdens for monitored workers. Under the linear dose–response model, the estimated ERR per gray of 5-year lagged cumulative external dose, adjusted for internal exposure, was 0.08 (90% CI 0.03; 0.14). As with lung, liver and skeletal cancers, the addition of a quadratic term in lagged cumulative dose revealed significant ($P = 0.05$) downward curvature in the dose response. Under this model, the estimate

TABLE 5
Observed and Expected Solid Cancer Deaths by External Dose Category with Estimates of Excess Cases from Both External and Internal Exposures

5-year lagged external dose category (Gy)	Person years	Observed	Expected	Excess deaths		
				External exposure	Internal exposure	Total
Lung, liver and skeletal cancers						
Unmonitored	131450	88	68.1	0	19.5	19.5
Zero	105281	3	4.2	0	1.1	1.1
−0.5	293390	198	146.3	13.0	52.8	65.8
−1	68233	82	45.1	16.4	18.0	34.4
−3	93685	205	72.5	57.3	58.3	115.6
−5	22678	68	20.5	26.0	24.8	50.8
5+	6958	24	6.7	8.6	8.8	17.4
Total	721703	668	363.4	121.3	183.3	304.6
Other solid cancers						
Unmonitored	131450	187	171.9	0	2.5	2.5
Zero	105281	9	16.9	0	0.3	0.3
−0.5	293390	400	373.8	12.5	9.5	22
−1	68233	111	114.4	15.4	3.8	19.2
−3	93685	267	182.0	49.7	13.6	63.3
−5	22678	62	51.0	18.8	5.7	24.5
5+	6958	26	16.0	2.4	1.8	4.2
Total	721675	1062	926.0	98.8	37.2	136.0
All solid cancers						
Unmonitored	131450	275	240	0	22	22
Zero	105281	12	21.1	0	1.4	1.4
−0.5	293390	598	520.1	25.5	62.3	87.8
−1	68233	193	159.5	31.8	21.8	53.6
−3	93685	472	254.5	107	71.9	178.9
−5	22678	130	71.5	44.8	30.5	75.3
5+	6958	50	22.7	11	10.6	21.6
Total	721675	1730	1289.4	220.1	220.5	440.6

of the low-dose slope was 0.21 (90% CI 0.06; 0.37), more than twice the slope of the linear model, with a downturn in the response at high doses. The right panel of Fig. 1 presents dose-category-specific (non-parametric) ERR estimates and shows both the fitted linear and linear-quadratic dose–response functions. Exclusion of workers in the surrogate categories with the highest potential for plutonium exposure had no appreciable effect on these results.

Migrants had significantly lower background rates ($P = 0.001$, SMR = 0.77; 90% CI 0.67; 0.87) than Ozyorsk residents, but there is no evidence of significant differences in the ERR per gray for these two groups ($P > 0.5$).

Attributable Risk Estimates

Table 5 summarizes the number of deaths and person years together with estimates of the numbers of deaths expected in the absence of exposure and of excess deaths associated with external and internal exposures in categories of 5-year lagged cumulative external dose. Estimates for lung, liver and skeletal cancers and other solid cancers were computed using the linear-quadratic ERR models for external exposure effects and a combination of the surrogate index for unmonitored workers and body burden for monitored workers. The results for all solid cancers are simply the sum of the estimates for lung, liver and skeletal cancers and other solid cancers.

The upper section of Table 5 suggests that almost half of the 668 lung, liver and skeletal cancer deaths are associated with radiation exposures and that roughly 40% of these deaths are linked to external exposures. The middle section of the table shows that only about 13% of the 1062 solid cancers are associated with radiation exposure. Three-fourths of the radiation-associated deaths were related to external exposures, but somewhat surprisingly, we estimated that about 37 of the 136 excess cases among these deaths are associated with internal exposures.

Effect Modification

The data on all solid cancers as a group were used to test for variation in the ERR with gender, age at hire (which was used as a surrogate for age at initial exposure), and time since exposure. There was no indication of a gender difference in the ERR for all solid cancers as a group ($P > 0.5$). The sex ratio (F:M) estimate was 1.0 (90% CI 0.3; 2.2) for the linear-quadratic dose–response model. There was no indication that the sex ratios for lung, liver and

TABLE 6
Time-Dependent Solid Cancer Mortality External Dose Risk Estimates

Years since external dose received	ERR/Gy[a]		
	Lung, liver or skeleton	Other solid cancer	All solid cancer
	Time-varying linear model		
5–10	<0.2 (<−0.3; 0.5)[b]	0.6 (−0.1; 1.25)	0.2 (−0.3; 0.7)
10–20	0.4 (−0.15; 0.9)	0.03 (−0.2; 0.3)	0.1 (−0.1; 0.3)
20+	0.6 (0.3; 0.9)	0.2 (0.08; 0.3)	0.3 (0.2; 0.4)
	Time-constant linear model (5-year lagged dose)		
Linear effect	0.30 (0.18; 0.46)	0.08 (0.03; 0.14)	0.15 (0.09; 0.20)
	Time-constant linear-quadratic model (5-year lagged dose)		
Linear effect	0.54 (0.27; 0.89)	0.21 (0.06; 0.37)	0.30 (0.18; 0.43)
Curvature	−0.10 (<−0.13; −0.01)	−0.14 (<−0.15; −0.05)	−0.12 (<−0.14; −0.06)

[a] Adjusted for plutonium exposure.
[b] 90% confidence interval.

skeletal or other solid cancers differ significantly from this estimate.

Solid cancer risks tend to decrease ($P = 0.05$) with age at hire. The decrease was estimated as 34% per decade (90% CI 6%; 60%). There was no indication that this effect differs for the two broad solid cancer groups that are the focus of this report.

We used linear models that allow different ERRs per gray in three time-dependent cumulative-dose windows to assess the influence of time since exposure on the ERR. While the individual estimates were quite variable (Table 6), there was no indication of statistically significant heterogeneity in the risks for all solid cancers ($P > 0.5$) or for either of the two cancer mortality subgroups, nor was there any evidence of a simple trend in the ERR with time since the dose was received.

Leukemia Risks

Table 7 presents the distribution of the 66 deaths from leukemia other than chronic lymphocytic leukemia (CLL) in categories of 2-year lagged cumulative dose. The table also presents estimates of the expected number of leukemia deaths based on an internal comparison for the time-dependent dose–response model in 2-year lagged cumulative dose (described below). It appears that about 40% of the non-CLL leukemia deaths are in excess of what one would expect. Inclusion of the plutonium-exposure surrogate measure provided no indication of a significant effect of plutonium on the leukemia risk estimates ($P > 0.5$), nor did the pattern of risk estimates suggest the presence of an exposure–response-like trend across the surrogate categories. The point estimate of the plutonium body burden dose response for monitored workers was negative but not statistically significant ($P > 0.5$)

There was a statistically significant ($P = 0.04$) increase in leukemia mortality risk with 2-year lagged cumulative external dose in a simple linear dose–response model without effect modification. The estimated ERR per gray was 0.99 (90% CI 0.45; 2.12). The addition of a quadratic term indicated a concave upward dose response, but it did not improve the fit significantly ($P = 0.1$). A pure quadratic model described the data as well as the linear-quadratic model.

There was no evidence of a significant sex difference in

TABLE 7
Observed and Expected Leukemia Deaths by External Dose Category with Estimates of Excess Cases from Both External and Internal Exposures

2-year lagged external dose category (Gy)	Person years	Observed	Expected	Excess deaths		
				External exposure	Internal exposure	Total
Unmonitored	131450.0	5	5.1	0	−0.1	−0.1
Zero	56727.8	1	2.1	0	0.1	0.1
−0.5	322779.0	23	16.9	3.4	0.4	3.8
−1	75025.2	8	4.9	3.4	0.2	3.6
−3	103073.0	13	7.6	10.6	0.5	11.1
−5	24971.5	9	2.2	5.2	0.1	5.3
5+	7649.0	7	0.7	2.7	0.0	2.7
Total	721675.5	66	39.5	25.3	1.2	26.5

TABLE 8
Time-Dependent Leukemia ERR per Gy Estimates

Years since dose received	ERR/Gy		
	Four periods	Two periods	One period
3–5 years	7.6 (3.2; 17)[a]	6.9 (2.9; 15)	1.0 (0.5; 2.0)
5–10 years	0.3 (<−0.1; 2.7)	0.45 (0.1; 1.1)	
10–20 years	0.8		
20+ years	0.4		

[a] 90% confidence interval.

the ERR ($P > 0.5$, female:male ratio 1.7 (90% CI 0.23; 11.2), nor was there significant change in the ERR with age at hire ($P = 0.2$). The estimated decrease in ERR per decade increase in age at hire was 46% with the 90% CI ranging from a 75% decrease to an 8% increase.

There was strong evidence of heterogeneity in the risk with respect to the time when the dose was received ($P = 0.01$), with the risk from doses received in the most recent 3 to 5 years being more than 10 times that from doses received more than 5 years ago. The ERR per gray estimates for cumulative doses in the four temporal windows are given in Table 8.

The 90% confidence bound for the risk of recently received doses was about (3.2; 17). There was little evidence of heterogeneity in risk with time for doses received more than 5 years previously ($P > 0.5$). The risk for doses received more than 5 years ago was much lower than the risk for more recent doses; the ERR per gray is 0.45 (90% CI 0.1; 1.1), and it was significantly greater than 0 ($P = 0.02$). There was no indication of any effects of external dose or internal exposure on the risks of CLL in this cohort ($P > 0.5$).

DISCUSSION

Long-term follow-up of the atomic bomb survivors has clearly demonstrated that acute exposure at low to moderate radiation doses leads to lifelong increases in cancer risks (*1, 2, 34*). However, the evidence for radiation effects on cancer risks after protracted, low-dose-rate exposures has been less compelling (*4*). Our analyses of cancer mortality in a large cohort of men and women with chronic, external, occupational exposure to γ rays provide the most convincing evidence to date of increased solid cancer and leukemia mortality after protracted, low-dose-rate exposures. These are the first analyses of the full Mayak worker cohort, including all periods of hire and including the newly added auxiliary plant workers whose radiation doses, while considerably lower than the main plant workers, tend to be larger than those of workers in other populations that have been studied. One reason that this study is able to detect effects of occupational exposures is that average worker doses of about 0.8 Gy are more than an order of magnitude higher than the average dose of 0.05 Gy reported in a large international pooled analysis of nuclear workers in the United States, United Kingdom, and Canada (*16*).

Gamma-ray risk estimation for the Mayak worker cohort is complicated by the fact that a large portion of workers in the radiochemical and plutonium production plants had the potential for significant internal exposures to α-particle radiation from inhalation of plutonium aerosols. A standardized program to measure plutonium body burdens was begun around 1970, but only about one-third of the workers with potential for plutonium exposure have been monitored. The 2.1-kBq mean body burden among monitored workers is considerably greater than body burdens reported for highly exposed workers in the United Kingdom (*35*) or United States. Because of this complication, recent efforts (*8, 11, 12*) to quantify lung cancer risks in this cohort have restricted analyses to subgroups of the cohort. To conduct a comprehensive evaluation of the risks associated with external γ-ray exposures, we expanded the cohort to include all male and female workers in the main plants hired from 1948 through 1972 and added a group of auxiliary plant workers with little or no radiation exposure. In addition, we developed a simple categorical occupational history-based surrogate index of plutonium exposure and used this index and, when available, plutonium body burden estimates to adjust external dose risk estimates for the possible effects of plutonium exposure.

After adjusting for internal exposure effects, we find statistically significant associations between γ-ray dose and the risks for the three broad groups of mortality from malignancies: lung, liver and skeletal cancer, other solid cancer and leukemia. Simple linear risk estimates indicate that, at a dose of 1 Gy, risks for lung, liver and skeletal cancers, as a group, are increased by about 15% while those for solid cancers in organs other than those most likely to concentrate plutonium are increased by about 8%. Our results suggest that risks per unit external dose might be higher in plutonium-concentrating organs than in other tissues, although it is possible that this reflects inadequate adjustment for plutonium exposure for these cancers. There are strong indications of nonlinearity in the risk. For both groups of solid cancers the dose response appears to be concave downward with risks per unit dose at low doses being about twice the linear estimates. Similar linear estimates are obtained when the population is limited to people with external dose estimates of less than 3 Gy. As suggested in refs. (*6*) and (*18*), it is likely that γ-ray doses may be overestimated in the early years because of a failure to properly account for the impact of high-energy β particles on the unshielded badges. This overestimation of the highest doses may partially explain the concave downward dose response. If so, the linear slopes in these linear-quadratic models may be a more appropriate estimates of the low-dose γ-ray effects. Atomic bomb survivor-based estimates (*1*) of the solid cancer mortality ERRs are about 0.45 for men and 0.9 for women exposed at age 25 (the average age at hire for members of the Mayak worker cohort). The Mayak esti-

mates described in this paper are somewhat lower than those for the atomic bomb survivors, but in view of the dosimetric uncertainties these comparisons should be regarded as very preliminary.

While there does not appear to be a gender difference in ERR for external exposure, there is a suggestion that the risk per unit dose decreases with increasing age at first hire. The estimated age-at-hire effect is similar to that seen in the atomic bomb survivors (*1*). However, this similarity should be interpreted cautiously since the Mayak workers received chronic exposures and the age-at-exposure range in the worker cohort is relatively narrow compared to the atomic bomb survivors. Solid cancer excess relative risks in this cohort do not appear to vary significantly with time since the dose was received. This is consistent with the generally constant relative risks seen for atomic bomb survivors who were exposed as adults.

Averaging over the full follow-up period, a dose of 1 Gy doubles the risk of non-CLL leukemia mortality. However, the data indicate that leukemia risks depend markedly on time since the exposure was received. Risks for recent exposures (dose received 3 to 5 years prior to death) appear to be an order of magnitude higher than those for dose from earlier exposures. We estimate that a dose of 1 Gy increases risks by about 700% in the period from 3 to 5 years after exposure and about 50% for periods more than 5 years after exposure. Despite the large difference in risk for doses received from recent and older exposures, we estimate that almost half (12 out of 25) of the external-radiation-associated leukemias are related to exposures that occurred more than 5 years prior to death. This pattern of high relative risks shortly after exposure and much lower risks associated with earlier exposures is quite comparable to the temporal patterns seen for leukemia risks in the atomic bomb survivors (*2*) and studies of medically exposed populations (*4*). There was no evidence of significant non-linearity in the leukemia dose response; however, correction of the dose estimates in the early years will tend to increase the evidence for upward curvature.

There are several sources of potential bias in risk estimates based on the Mayak worker cohort. As noted earlier, one area of concern involves differences in autopsy rates for workers in different plants or periods. We investigated the possibility of bias associated with autopsy rate differences by taking advantage of the fact that autopsy rates for migrants are considerably lower than those for Ozyorsk residents (indeed this difference in rates is considerably greater than the differences associated with plant or radiation dose among Ozyorsk residents). Our results suggest that differential autopsy rates cannot explain the significant γ-ray dose response nor are they likely to bias the risk estimates.

Smoking is often considered as a potential confounding factor in radiation risk estimation, especially for lung cancer. Complete information on smoking habits of cohort members is not currently available. The limited data available suggest that while smoking rates were quite high for men, the correlations between smoking and radiation dose or plutonium body burden are weak. Thus we think that failure to adjust for smoking does not lead to an artifactual association with radiation dose in this population.

Occupational exposure to carcinogenic compounds is another potential confounding factor, but unfortunately we have little information at this time on the nature of such exposures and no useful data on the correlation between these exposures and radiation dose. To learn more about potential chemical exposures, we examined internal reports prepared by the Biophysics Institute, Branch 1 (currently the South Urals Biophysics Institute) industrial hygienists throughout the period of Mayak's operation, and consulted with the head of the SUBI industrial hygiene laboratory (F. D. Tretyakov, personal communication). According to information from these sources, it appears unlikely that exposure to other carcinogens accounts for—or seriously biases—the radiation risk estimates. There was no known exposure to beryllium at the Mayak facilities included in this study. While asbestos was used for insulation in some areas of all Mayak plants, Dr. Tretyakov indicated that there was no appreciable asbestos exposure to workers in this cohort. However, eight of the 56 ''other respiratory'' cancers are mesotheliomas, and all of these occurred among workers in the radiochemical or plutonium production plants. The apparent lack of asbestos exposure suggests that plutonium may play a role in the etiology of mesothelioma. These findings warrant further investigation.

In this paper, we have not attempted to evaluate risks for solid cancers of specific sites. Studies of other populations exposed to whole-body radiation (such as the A-bomb survivors) have usually included the broad category of all solid cancers (or all cancer excluding leukemia) because this allows more precise estimation of model parameters than would be possible for individual sites. We note also that Pierce *et al.* (*1*) found little evidence of heterogeneity among ERR models developed for 13 specific cancer sites based on atomic bomb survivor mortality data. Nevertheless, our models are not necessarily appropriate for each of the contributing sites, and it will be important to investigate variation by site in the future as the numbers of deaths increase and dose estimates are improved. We note particularly that lung cancer dominates the lung, liver and skeletal cancer category, so this model may be more relevant for lung cancer than for cancers of the liver and skeleton. To look at this issue, we plan to conduct detailed analyses of each of these sites using estimated organ doses from plutonium.

As discussed above, to estimate (external) γ-ray dose effects, we have adjusted for the effects of internal exposure using a combination of a categorical index of potential for plutonium exposure for unmonitored workers and plutonium body burden estimates for monitored workers. This approach allows us to compute useful estimates of the number of internal exposure-associated cases and information about the existence of a dose response for internal exposures, but

it does not provide useful quantitative risk estimates for the effects of plutonium exposure. We found strong evidence of a dose response for internal exposures for deaths due to cancers of the organs of primary plutonium deposition (lung, liver and skeleton) and all solid cancers as a group. Surprisingly, the data also suggest a smaller but still statistically significant effect of internal exposure on the risk of death for cancers in organs other than the lung, liver and skeleton. There was no indication of any effect of internal exposures on leukemia mortality. This is consistent with the apparent absence of an increase in leukemia risks among radium dial painters who also had high cumulative exposures from deposition of α-particle emitters on the bone surface (*36*, *37*). The reasons for these unexpected findings regarding solid cancers other than those in the lung, liver, and skeleton are unclear since both theoretical computations and autopsy measurements (*20*) suggest that plutonium deposition leads to relatively little exposure (or dose) to tissues other than those of primary deposition. One possibility is that these increased risks may reflect a nonspecific effect on the body's ability to deal with other cancer risk factors in the face of chronic low-dose-rate exposure.

A major strength of the Mayak worker cohort is the high-quality follow-up. Over a follow-up period ranging from 30 to 50 years, less than 10% of the cohort members have been lost to follow-up, and documented cause of death is available for about 97% of the deaths. The relatively large number of heavily exposed female workers is also an important feature of the Mayak worker cohort. Current uncertainties about internal and external dose estimates are the study's major limitation. Despite these dosimetric uncertainties, the Mayak worker cohort provides useful, new estimates of the risks associated with chronic γ-ray exposure. With the expected improvements in external dose estimates and characterization of internal exposures and doses, this cohort will yield more precise and more comprehensive risk estimates over the next few years.

ACKNOWLEDGMENTS

The authors would like to thank Dr. V. F. Khokhryakov, the head of the SUBI Internal Dosimetry Laboratory for providing data on plutonium body burden and doses from plutonium. Support for this study has been provided by the United States National Cancer Institute through contracts N01-CP-81034 and N01-CP-51025 and by the Russian Ministry of Health.

Received: October 28, 2002; accepted: February 6, 2003

REFERENCES

1. D. A. Pierce, Y. Shimizu, D. L. Preston, M. Vaeth and K. Mabuchi, Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat. Res.* **146**, 1–27 (1996).
2. D. L. Preston, S. Kusumi, M. Tomonaga, S. Izumi, E. Ron, A. Kuramoto, N. Kamada, H. Dohy, T. Matsuo and K. Mabuchi, Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat. Res.* **137** (Suppl.), S68–S97 (1994).
3. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Terasaki and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
4. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation.* 2000 Report to the General Assembly, with Scientific Annexes. United Nations, New York, 2000.
5. N. A. Koshurnikova, N. S. Shilnikova, P. V. Okatenko, V. V. Kreslov, M. G. Bolotnikova, S. A. Romanov and M. E. Sokolnikov, The risk of cancer among nuclear workers at the ''Mayak'' production association: Preliminary results of an epidemiological study. In *Implications of New Data on Radiation Cancer Risk,* Proceedings of the Thirty-Second Annual Meeting of the National Council on Radiation Protection and Measurements held April 3–4, 1996. National Council on Radiation Protection and Measurements, Bethesda, MD, 1997.
6. N. A. Koshurnikova, N. S. Shilnikova, P. V. Okatenko, V. V. Kreslov, M. G. Bolotnikova, M. E. Sokolnikov, V. F. Khokhriakov, K. G. Suslova, E. K. Vassilenko and S. A. Romanov, Characteristics of the cohort of workers at the Mayak nuclear complex. *Radiat. Res.* **152**, 352–363 (1999).
7. N. A. Koshurnikova, E. S. Gilbert, N. S. Shilnikova, M. Sokolnikov, D. L. Preston, M. Kreisheimer, E. Ron, P. Okatenko and S. A. Romanov, Studies on the Mayak nuclear workers: Health effects. *Radiat. Environ. Biophys.* **41**, 29–31 (2002).
8. Z. B. Tokarskaya, N. D. Okladnikova, Z. D. Belyaeva and E. G. Drozhko, Multifactorial analysis of lung cancer dose-response relationships for workers at the Mayak nuclear enterprise. *Health Phys.* **73**, 899–905 (1997).
9. Z. B. Tokarskaya, N. D. Okladnikova, Z. D. Belyaeva and E. G. Drozhko, The influence of radiation and nonradiation factors on the lung cancer incidence among the workers of the nuclear enterprise Mayak. *Health Phys.* **69**, 356–366 (1995).
10. V. F. Khokhryakov, A. M. Kellerer, M. Kreisheimer and S. A. Romanov, Lung cancer in nuclear workers of Mayak. A comparison of numerical procedures. *Radiat. Environ. Biophys.* **37**, 11–7 (1998).
11. N. A. Koshurnikova, M. G. Bolotnikova, L. A. Ilyin, I. B. Keirim-Markus, Z. S. Menshikh, P. V. Okatenko, S. A. Romanov, V. I. Tsvetkov and N. S. Shilnikova, Lung cancer risk due to exposure to incorporated plutonium. *Radiat. Res.* **149**, 366–371 (1998).
12. M. Kreisheimer, N. A. Koshurnikova, E. Nekolla, V. F. Khokhryakov, S. A. Romanow, M. E. Sokolnikov, N. S. Shilnikova, P. V. Okatenko and A. M. Kellerer, Lung cancer mortality among male nuclear workers of the Mayak facilities in the former Soviet Union. *Radiat. Res.* **154**, 3–11 (2000).
13. E. S. Gilbert, N. A. Koshurnikova, M. Sokolnikov, V. F. Khokhryakov, S. Miller, D. L. Preston, S. A. Romanov, N. S. Shilnikova, K. G. Suslova and V. V. Vostrotin, Liver cancers in Mayak workers. *Radiat. Res.* **154**, 246–252 (2000).
14. N. A. Koshurnikova, E. S. Gilbert, M. Sokolnikov, V. F. Khokhryakov, S. Miller, D. L. Preston, S. A. Romanov, N. S. Shilnikova, K. G. Suslova and V. V. Vostrotin, Bone cancers in Mayak workers. *Radiat. Res.* **154**, 237–245 (2000).
15. N. S. Shilnikova, D. L. Preston, E. K. Vassilenko, E. Gilbert, E. Ron and N. A. Koshurnikova, Cancer risk among workers at the Russian Nuclear Complex Mayak. In *Radiation Research,* Vol. 2 (M. Moriarty, C. Mothersill, C. Seymour, M. Edington, J. F. Ward and R. J. M. Fry, Eds.), pp. 766–769. Allen Press, Lawrence, KS, 2000.
16. E. Cardis, E. S. Gilbert, L. Carpenter, G. Howe, I. Kato, B. K. Armstrong, V. Beral, G. Cowper, A. Douglas and J. Fix, Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat. Res.* **142**, 117–132 (1995).
17. *International Classification of Diseases: Manual of Statistical Classification of Diseases, Injuries, and Causes of Death*, 1975 Revision, Vol. 1. World Health Organization. Geneva, 1977.
18. V. Khokhryakov, K. Suslova, E. Aladova, E. Vasilenko, S. C. Miller, D. M. Slaughter and M. P. Krahenbuhl, Development of an improved dosimetry system for the workers at the Mayak Production Association. *Health Phys.* **79**, 72–76 (2000).

19. ICRP, *Limits for the Intake of Radionuclides by Workers.* Report of Task Group of Committee 2 of the International Commission on Radiological Protection. Pergamon Press, Oxford, 1979.

20. K. G. Suslova, V. F. Khokhryakov, Z. B. Tokarskaya, A. P. Nifatov, M. P. Krahenbuhl and S. C. Miller, Extrapulmonary organ distribution of plutonium in healthy workers exposed by chronic inhalation at the Mayak production association. *Health Phys.* **82**, 432–444 (2002).

21. V. F. Khokhryakov, S. A. Romanov and K. G. Suslova, A model of lung clearance of plutonium. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (G. Van Kaick, A. Karaoglou and A. M. Kellerer, Eds.), pp. 117–121. World Scientific, Singapore, 1995.

22. V. F. Khokhryakov, Z. S. Menshikh, K. G. Suslova, K. G. Kudryavtseva, Z. B. Tokarskaya and S. A. Romanov, Plutonium excretion model for the healthy man. *Radiat. Prot. Dosim.* **53**, 235–239 (1994).

23. V. F. Khokhryakov, K. G. Suslova, I. A. Tsevelyova, E. E. Aladova and R. E. Fillipy, Classification of alpha-active workplace aerosols based on coefficients of transportability as measured by the dialysis method. *J. Radioanal. Nucl. Chem.* **234**, 209–212 (1998).

24. K. G. Suslova, V. F. Khokhryakov, Z. B. Tokarskaya, T. I. Kudryavtseva and A. P. Nifatov, Plutonium distribution in organs of the extrapulmonary pool long after beginning of inhalation in workers at radiochemical production. *Med. Radiol. Radiat. Safety* **1**, 17–25 (2000). [in Russian]

25. L. A. Buldakov, E. R. Lubchansky, Y. I. Moskalev and A. P. Nifatov *Problems of Plutonium Toxicology* Atomzidat, Moscow, 1969. [in Russian]

26. J. F. McInroy, R. L. Kathren and M. J. Swint, Distribution of plutonium and americium in whole bodies donated to the United States Transuranium Registry. *Radiat. Prot. Dosim.* **26**, 151–158 (1989).

27. F. A. Mettler and A. C. Upton, *Medical Effects of Ionizing Radiation,* 2nd ed. W. B. Saunders, Philadelphia, 1995.

28. D. A. Pierce and D. L. Preston, Joint analysis of site-specific cancer risks for the atomic bomb survivors. *Radiat. Res.* **134**, 134–142 (1993).

29. D. Preston, J. Lubin, D. Pierce and M. McConney, *Epicure Users Guide.* Hirosoft, Seattle, WA, 1993.

30. H. A. Weiss, S. C. Darby, T. Fearn and R. Doll, Leukemia mortality after X-ray treatment for ankylosing spondylitis. *Radiat. Res.* **142**, 1–11 (1995).

31. J. D. Boice, Jr., M. Blettner, R. A. Kleinerman, M. Stovall, W. C. Moloney, G. Engholm, D. F. Austin, A. Bosch, D. L. Cookfair and E. T. Krementz, Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J. Natl. Cancer Inst.* **79**, 1295–1311 (1987).

32. R. E. Curtis, J. D. Boice, Jr., M. Stovall, L. Bernstein, R. S. Greenberg, J. T. Flannery, A. G. Schwartz, P. Weyer, W. C. Moloney and R. N. Hoover, Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N. Engl. J. Med.* **326**, 1745–1751 (1992).

33. R. E. Curtis, P. A. Rowlings, H. J. Deeg, D. A. Shriner, G. Socie, L. B. Travis, M. M. Horowitz, R. P. Witherspoon, R. N. Hoover and J. D. Boice, Jr., Solid cancers after bone marrow transplantation. *N. Engl. J. Med.* **336**, 897–904 (1997).

34. D. A. Pierce and D. L. Preston, Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat. Res.* **154**, 178–186 (2000).

35. R. Z. Omar, J. A. Barber and P. G. Smith, Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br. J. Cancer* **79**, 1288–301 (1999).

36. F. W. Spiers, H. F. Lucas, J. Rundo and G. A. Anast, Leukaemia incidence in the U.S. dial workers. *Health Phys.* **44** (Suppl.), 65–72 (1983).

37. J. H. Stebbings, Radium and leukemia: Is current dogma valid? *Health Phys.* **74**, 486–488 (1998).